

# Females in Clinical Studies: Where are We Going?

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Historically females of all ages have been underrepresented in clinical research. Reasons for this exclusion are multifactorial and may possibly have their origins in regulation that forbid the participation of females of childbearing potential in the earliest phase clinical studies that support drug approval. Decades of female underrepresentation in clinical studies has resulted in inequality in the understanding, diagnosis, and treatment of disease between the sexes. Adequate numbers of both sexes is one approach which is likely to present overwhelming financial constraints. Advances in study design, statistical methodologies, and the promise of evolving technologies will lead to new tools that can foster a better understanding of the biology that governs sex and gender differences.

While the deadline for this editorial was looming, an Institutional Review Board member from a prestigious academic institution phoned inquiring about Food and Drug Administration (FDA) regulations regarding the participation of females of childbearing potential (FCBP) in clinical studies. She described a situation in which the commercial sponsor proposed to exclude FCBP from a study of a topical drug. The drug has no detectable systemic absorption and no adverse reproductive outcomes in animal reproductive toxicology studies. There appeared to be no compelling rationale to exclude FCBP from the study. Her query, however, is worth reflecting upon. Why in the early 21st century do we still see females excluded from studies? Perhaps it is that old habits die hard, making re-examination of the history of females in clinical studies essential for moving forward.

Females have been excluded from clinical studies since the beginning of modern clinical trial design—a condition that is unique neither to drug studies nor to research conducted in the United States. Until the last quarter of the 20th century, sex<sup>1</sup> was not recognized as a variable in health research, nor was it believed to be a factor that could affect health and

illness. Health researchers preferred studying males for reasons such as:

- simplicity—females were perceived as “harder” to study.
- lower costs—decreased sample size to preserve sex homogeneity.
- paternalism—desire to protect females and the fetus.
- fear of liability from perinatal exposure should pregnancy occur.
- concern about confounding effects of hormonal and reproductive issues.

In 2001, the Institute of Medicine concluded that sex should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research.<sup>1</sup> National Institutes of Health (NIH) has a long history of involvement with issues pertinent to the recruitment and retention of women in clinical research—including the 1987 NIH policy that encouraged the inclusion of women and minorities, the 1990 creation of the Office of Research on Women's Health, the 1993 NIH Revitalization Act making into law the inclusion of women and minorities in all NIH-supported research, as well as numerous public workshops and reports.<sup>2</sup> Several surveys have looked at the participation of females from a regulatory perspective by reviewing studies submitted to FDA.<sup>3</sup> An internal FDA survey of Investigational New Drugs (INDs) and New Drug Applications (NDAs) (1992–1996) determined that females, regardless of childbearing potential, were ineligible to participate in approximately 25% of studies reviewed, with 40% of the exclusions in phase I pharmacokinetic studies. Although females had not been widely excluded from participating in studies, their inclusion tended to be late in drug development. For some product areas, females were not represented in studies in proportion to the disease prevalence in females; the patient population used to support approval of cardiac drugs was predominantly (~2/3) male. A similar review in 2001 by the Government Accounting Office (<http://www.gao.gov/new.items/d01754.pdf>) reported that slightly less than half

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(44%) of new molecular entity NDAs submitted to FDA in a 2-year period contained sufficient numbers of females to demonstrate statistically that the drug was effective in females and that 52% of study participants were in fact females. However, females were again underrepresented in some areas, such as cardiac drug studies and phase I pharmacokinetic studies.

FDA's earliest written policy on inclusion of females in clinical studies—or more accurately, their exclusion—was largely a result of the 1960s thalidomide birth defect epidemic. Public fear of another such event was palpable at the time, leading FDA to require information in product labels about drug risk in pregnancy, and to look closely at inclusion of FCBP in clinical studies. In 1977, FDA issued a guideline recommending that FCBP be excluded from the earliest clinical studies. It suggested that FCBP could participate in clinical studies if adequate information on efficacy and relative safety was obtained during early phase II and if animal fertility and teratology studies were completed and found, reassuring no fetal risk. The use of contraception to avoid pregnancy was not addressed. For years there was little controversy about this paradigm.

Rapid growth of drug development science, especially in the face of dire societal need for treatments of HIV and cancer, reframed public thinking. Critics argued that the 1977 guideline, precluded a female's ability to make decisions that affected her life, violating the informed consent principle of participant autonomy. Advocacy groups asserted that females were denied access to important and innovative therapies, many of which were only available in clinical studies. In 1993, FDA revoked the 1977 guideline, acknowledging that fetal exposure could be prevented by appropriate protocol design and contraception. The 1993 guideline<sup>4</sup> recommended that effectiveness and adverse effects of a drug be analyzed by sex and that pharmacokinetics be defined in males and females. In 1998, FDA amended the NDA and IND regulations (21 CFR 314.50 and 21 CFR 312.33) to require that NDAs contain information on trial participation, safety, and effectiveness for important demographic groups such as gender, age, and racial subgroups, and that IND annual reports tabulate the number of participants enrolled according to gender, age, and race. Thus, although FDA regulations are often cited as a major reason why females continue to be less than adequately represented in clinical studies, these facts suggest there is more to the story.

Medical research is naturally influenced by society itself; as members of society ourselves, the influences can be so ingrained, that they are often difficult to see. This may help explain our limited understanding of the pathophysiology, diagnosis, and treatment of many diseases in females and why change to include females in clinical studies has been slow. An example of this is the Framingham study, probably the best-known large-scale epidemiology study of coronary heart disease (CHD). If only science was involved, one might expect that the rationale to study only males was because investigators believed that females were not subject to heart

disease. This seems unlikely. Was it because including females would be difficult, complicated, or messy? Assuming that data from males could easily be extrapolated to females was possibly the reason. Any of these explanations might apply when the Framingham study began in 1948. However, an Agency for Healthcare Research and Quality (AHRQ) review<sup>5</sup> of published literature from 1985–2001 pertinent to CHD reported that much of the research on diagnosis and treatment of CHD either excluded females entirely or included only limited numbers. This research paradigm cost society dearly. It has taken decades to discover that females have different disease patterns, signs, symptoms, and responses to treatment for CHD than males. Lack of or inadequate female participation in studies has historically extended to other medical conditions as well, including HIV.<sup>6</sup>

We must acknowledge that research to understand sex differences is not always best served by simply including an adequate number of both sexes in clinical studies, which is often inadequate to enable a scientifically based understanding of sex differences in safety and efficacy. It is more likely that such subgroup analyses may lead to hypotheses about reasons for and the consequences of sex differences that will require further investigation. Nonetheless, even such basic assessments are often not carried out. The AHRQ review found that only 20% of the articles reviewed for CHD provided findings specific to females. A Cochrane Analysis of 117 HIV studies found only one study that provided data by sex, seven studies (6%) specified a stratified analysis by sex, and one mentioned sex/gender-related information in the Results and Discussions section.

Perhaps part of the struggle to understand whether there are sex/gender differences in response to diagnostics and interventional treatments is that study design and statistical requirements to go beyond a rough estimate of differences are often overwhelming. They necessitate careful and innovative advance planning, recruitment, and statistical strategies so that differences (or similarities) observed by sex are interpretable. Further complicating matters is that biologically, females are not a homogenous population. The effect of ovarian hormones on physiology and response to any type of intervention in premenarchal females, FCBP, and peri- and postmenopausal females is poorly understood. FCBP themselves encompass a wide spectrum of age that includes adolescent females, who, for many purposes, are considered children. Knowledge of important age differences in neuroendocrine growth and development and drug metabolism is already driving forces for studies of adolescents in disease areas such as depression. From a practical standpoint, what begins as a simple analysis of clinical study data by sex, quickly becomes complicated when the age range of subjects is wide.

If societal values and perspectives are major drivers of scientific inquiry, rising expectations for “personalized medicine” may facilitate robust inquiry to the effects of sex/gender on disease manifestations and treatment. Medicine cannot get any more “personal” than an appropriate

understanding of disease, diagnosis, and treatment based on an individual patient's demographics. Advances in study design, statistics, and the promise of “-omic” technologies will further develop new tools that foster a better understanding of the biology that governs sex/gender differences. Implementing these tools will necessitate innovative recruitment and retention methodologies in clinical studies and will surely require robust representation of both sexes, regardless of age and other demographics. Thus, crude though we may find the simple metric of balanced representation of both sexes in clinical studies, vigilant attention to it remains our best tool for allowing new methods to be applied. It is incumbent upon us in our various roles—as investigators, journal reviewers and editors, scientific review committee members, and grant reviewers—to actively challenge ingrained residual scientific habits. It is time to recognize that sex is an important variable in biomedical research and advocate not only for adequate numbers of both males and females, but also for more rational and scientific approaches to the study of sex/gender differences. Recognizing our past is good, understanding it to move forward is even better.

#### CONFLICT OF INTEREST

The authors declared no conflict of interest.

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